5-Azacitidine:
An Alternative Treatment of Myelodysplastic Syndromes in Patient with Refractory Response to Hematopoietic Growth Factor
A Case Report and Review of Literatures

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Abstract

Myelodysplastic Syndrome (MDS) comprises a heterogeneous group of clonal hemopathies derived from an abnormality affecting a multipotent hematopoietic stem cell and characterized by maturation defects resulting in ineffective hematopoiesis. It most frequently occurs in elderly patients. Despite trials testing numerous agents in patients with MDS, no single drug has yet emerged as the accepted standard of treatment. Most MDS patients, due to their age and co morbidity, are not eligible for allogeneic hematopoietic stem cell transplantation; the only established curative regimen. The effect of available lineage-specific growth factors is limited to improvement of single lineages and has not resulting in the survival benefit. Treatment with low dose Ara-C is disappointing in regard to response rate or duration. No benefit has been demonstrated in differentiation inducers such as retinoids and Vitamin D3 as single agents. We report a case of a patient with transfusion dependent MDS who was not a candidate for allogeneic stem cell transplantation or cytotoxic chemotherapy, who also failed to response to erythropoietin support but had a favorable response to 5-azacitidine. His blood transfusion requirement reduced significantly, and was correlated with the remarkable improvement of the pancytopenia, particularly anemia and thrombocytopenia after receiving the investigational therapy with 5-azacitidine. In summary, 5-azacitidine appears to be a promising alternative therapy for patient with refractory anemia secondary to MDS.

Introduction

Myelodysplastic Syndrome (MDS) comprises a heterogenous group of clonal hemopathies derived from an abnormality affecting a multipotent hematopoietic stem cell. MDS is characterized by the maturation defects resulting in the ineffective hematopoiesis and various combinations of cytopenia, including, but not limited to anemia, leukopenia, and thrombocytopenia.[1-4] It most frequently affects the elderly patients, with greater than 80% of patients being older than 60 years of age. In the population beyond 70 years of age, the incidence of MDS is approximately 22-45 per 10,000 population, indicating MDS is as prevalent as the other most common hematologic malignancies of the aged.[3] Despite trials testing numerous agents in patients with MDS, no single drug has yet emerged as accepted standard of treatment. Most MDS patients, due to their age and co morbidity, are not eligible for allogeneic hematopoietic stem cell transplantation, the only established curative regimen. The effect of the available recombinant lineage-specific hematopoietic growth factors are limited to the improvement of only single lineages and have not resulted in the survival benefit. The treatment option of low dose Ara-C is disappointing in regard to either survival or transformation to AML.[7] There has been no benefit demonstrated for differentiation inducers such as retinoids and vitamin D3, as the single agent therapy.[11] We describe a patient with transfusion dependent MDS who failed hematopoietic growth factor (erythropoietin) but has had a favorable response to 5-azacitidine resulting in the significant improvement of anemia and thrombocytopenia as well as the remarkable reduction of blood transfusion requirement.

Report of a Case

A 75 year-old man presented to the hematology clinic, referred by his primary care physician for further evaluation of anemia. He was noted to have a mild anemia (Hb 11.9 g/dl and Hct 35% with MCV 92.6) during his annual physical examination. Patient was asymptomatic at the time. There was no history of blood loss, peptic ulcer disease, bowel habit change, weight loss or ulcerogenic drug use. His pertinent medical history consisted of hypercholesterolemia treated with a lipid lowering agent, childhood asthma and chronic nasal allergy. His physical examination was unremarkable and without lymphadenopathy or organomegaly. Other laboratory findings included a mild leukopenia (WBC 2,900/mm^3) with a normal

platelet count. The peripheral blood smear revealed normal red blood cell, white blood cells and platelet morphology. The CBC drawn seven years earlier revealed a Hb and Hct 16.2 g/dl and 46.9%, respectively. Further laboratory work up, including Iron study, Folate, Vitamin B 12 level, and TSH, were all normal. At the time, clinical observation and regular CBC monitoring were recommended, given that he was clinically stable without anemia or leukopenia-related symptoms.The follow up Hb and Hct remained stable (Hb and Hct were in the range of 12.6-13.8 g/dl and Hct 38.3-40.6 %, respectively) without any treatment until three years later when the patient was noted to have a further decline in Hb and Hct (Hb 9.6 g/dl and Hct 29.8%, MCV 94). In addition, CBC was also remarkable for worsening leukopenia (WBC 2,400/mm^3 with normal differential count). The peripheral blood smear showed 2+ anisocytosis with increased macrocytes. The bone marrow aspiration and biopsy was then performed. The pathology report included 35% cellularity with patchy marrow fibrosis. The erythroid precursors revealed normoblastic erythroid hypoplasia with adequate stainable iron. There was an evidence of left-shifted granulopoiesis with delayed maturation and dysmegakaryopoiesis. The pathologic findings strongly favored MDS, refractory anemia (RA) subtype. Hematopoietic Growth Factor, (erythropoietin), initially at 10,000 units given subcutaneously thrice weekly was then begun and continued for four months. The erythropoietin dose was subsequently increased to 20,000 units given twice weekly for another four months due to no significant reduction in packed red blood cell transfusion requirement or improvement of Hb/Hct, which dropped to as low as 5.8 g/dl and 17.2%, respectively. During the follow up, the patient later developed profound thrombocytopenia with platelet counts ranged between 7,000 and 90,000 /mm^3 . Consequently, a repeat bone marrow examination was performed. The findings revealed hypocellularity, dyshematopoiesis, progression of marrow fibrosis, bicytopenia and persistent dysplastic change without evidence of blastic transformation, consistent with the prior diagnosis of MDS. At this point, the patient's quality of life was severely affected by the anemia secondary to MDS. Since he was deemed not to be a good candidate for more aggressive therapy, including the allogeneic stem cell transplantation, alternative treatment with investigational agent; 5-azacitidine was considered. Five-azacitidine was started under the compassionate release protocol from the NIH. The treatment schedule consists of 75 mg/m^2 of 5-azacitidine given subcutaneously everyday for 7 days per cycle as an outpatient treatment. The treatment course was repeated every twenty-eight days for six cycles and an additional two cycles with 50% dose-reduction were given after the completion of the sixth cycle. Following the third course of 5-azacitidine, a remarkable improvement in the pancytopenia, particularly the anemia and thrombocytopenia, was demonstrated. The Hb rose to as high as 11.8 g/dl with Hct to 34.2%, a major progress comparing with that observed during the erythropoietin therapy.The requirement for packed red blood cell transfusion also declined dramatically and correlated with the response in the Hb and Hct. However, the most notable laboratory response was seen in the platelet count, which displayed in the range of 104,000-536,000/mm^3 . These hematologic responses to the treatment have been maintained for months after the discontinuation of the medication. During the course of the treatment, the reported adverse effects included mild leukopenia without neutropenia (WBC 1,800-3,600/mm^3) which resolved prior to the next administration of 5-azacitidine; mild nausea and vomiting relieved with antiemetics. The liver and renal function tests remained normal throughout the course of the therapy.

Discussion

To date there are no curative therapeutic options for patients with MDS, with the exception of intensive chemotherapy with allogeneic stem-cell transplantation, available to a minority of young patients. The data from clinical trials employed intensive chemotherapy with autologous hematopoietic stem cell support is limited and its value remains to be proven. The response duration is often short and the relapse rate is high.[14] There is no survival benefit seen in a randomized trial comparing low-dose cytarabine with supportive care alone.[7] Topoisomerase I inhibitors have gained interest but they are reported with the substantial toxicity. Cell-differentiation therapy with either retinoids or vitamin D3 analogs has yielded disappointing results. Other approach, including the use of lineage-specific growth factors, such as erythropoietin, G-CSF, or GM-CSF has provided only the limited improvement of the single lineages and has not resulted in the survival benefit.[11] Unfortunately, the majority of patients with MDS are elderly and often have serious underlying co-morbidities, which may preclude them from participating in the more aggressive therapy, especially the allogeneic stem celll transplantation. For these patients, the novel therapeutic approach is needed and should be aimed at eradication or suppression of the abnormal clone or induction of cell differentiation of the pre-malignant clone.

Five-Azacitidine(azacitidine), the ring analogue of the pyrimidine nucleoside cytidine, first synthesized in 1964 by Sorm and co-worker, has been clinically developed based on the strong in vitro and in vivo antileukemic activity at cytotoxic concentrations, and differentiation-inducing potential at lower concentrations in cell line models of hematopoietic and non-hemato-poietic lineages.[6,9] The mechanism of action

is believed to be distinct from those of other pyrimidine antimetabolites, including Ara-C, suggested by the lack of severe bone marrow hypoplasia preceding the hematologic reponses to low-dose azacitidine in myelodysplasia. Following its phosphorylation to monophosphates, 5-azacitidine is incorporated into newly synthesized DNA resulting in hypomethylated DNA strand synthesis.[6] As recently reviewed, cytosine hypermethylation of numerous genes important in orderly cell proliferation and maturation is frequent in primary neoplasia and tumor cell lines. Therefore, the application of pharmacologic inhibitors of DNA methylation provides a theoretically rational approach to regress these epigenetic changes in the malignant clone and re-establishing the antiproliferative and possibly differentiation-inducing signals silenced by hypermethylation.[15] In MDS, the disturbed maturation of the morphologically dysplastic hematopoietic cells is thought to reflect a partial block in their differentiation with proliferation of preleukemic myeloblasts, providing a rationale for clinical trials of DNA methylation inhibitors. Five-azacitidine has shown activity in approximately 50% of MDS patients in several uncontrolled studies published since 1984, with two phase-II trials and a single phase-III study, initiated by the Cancer and Leukemia Group B (CALGB) in 1984, 1989 and 1994, respectively.[6] In the CALGB 8421 trial, a continuous infusion of azacitidine 75 mg/m^2 for seven days, repeated every 28 days, resulted in a 49% response rate with 12% complete remission (CR*), 25% partial remission (PR*) and 12% hematological improvement (HI*).[10] In addition, the complete elimination of all transfusion requirements occurred in 82% of the patients, while another 18% had a greater than 50% reduction in the number of units required per month. In the CALGB 8921 trial reported by Silverman et al, azacitidine given at the same total dose was administered by daily subcutaneous bolus injection, thus allowing for outpatient treatment.[18] This resulted in a 53% overall response rate (12% CR, 15% PR and 27% HI). The median time to response was 4.5 treatment courses. The median response duration was 17.3 months. These two clinical trials were performed in high-risk MDS patients. However, there was a relatively lower rate of trilineage response with subcutaneous administration of azacitidine (27% VS 37%). Rugo et al also treated 92 patients, most of them with high-risk MDS (60% were classified as refractory anemia with excess blasts;RAEB in transformation or chronic myelomonocytic leukemia) or secondary AML, with the same outpatient schedule of 75mg/m^2 /D given subcutaneously for 7 days, repeated every twenty-eight days for six cycles.[16] In a retrospective analysis, they reported a 61% response rate (13% CR and 19% PR). Two patients with complete hematological response also had a cytogenetic remission. The significant improvement in quality of life and well-being in patients treated with azacitidine was demonstrated in a randomized phase-III study done by CALGB in 1998, using the identical dose and subcutaneous route.[17] In this study, response rate, survival and time to progression to AML in treated patients were compared with a patient group assigned to a four-month observation period. Study design allowed cross over to the treatment arm after 4 months in those with disease progression. The response rate in the treatment group was 63% and the probability of transformation to AML was 11%, compared with a 31% transformation rate in patients on observation, which was statistically significant (P=0.003). The common adverse effects are GI toxicity, which is usually mild, including nausea and/or vomiting, followed by diarrhea. Other side effects were less frequent and included elevation of hepatic transaminase enzymes and confusion.

Conclusion

5-azacitidine has demonstrated significant activity in ameliorating or even temporarily correcting both the deficits in peripheral blood counts of all three lineages and the pre-leukemic blast excess in high-risk MDS. This combination of activities, the convenient outpatient treatment schedule as well as the mild adverse reaction profile makes this drug distinctively promising. In elderly patients with MDS who frequently have significant co-morbidities, this low-intensive, low toxicity therapy may be an optimal alternative.

*CR: Complete response was defined as full normalization of all three peripheral blood counts and less than 5% myeloblasts in bone marrow

*PR: Partial response was defined as achieving a greater than 50% restoration of the deficit from normal in each of the three peripheral blood counts and absence of myeloblasts in peripheral blood, the elimination of transfusion requirements, and decrease in percentage of myeloblasts in the bone marrow by 50%

HI*: Hematological improvement; greater than 50% restoration in the deficit from normal in either red cell, white cell, or platelet counts and/ or at least 50% decrease in the transfusion requirement from baseline.

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